Brief overview of Breast cancer: Past, Present and Future

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Article Info: Received 18 Sep 2016; Revised: 27 Nov 2016; Accepted 11 Dec 2016.

ABSTRACT

Breast cancer is the most common cause of cancer-related deaths in women worldwide. This disease has always challenged physicians since ancient times. Once, surgery was ruled as primary therapy to get rid of breast cancer, now time have changed and several novel therapies reached to the clinics that helped avoiding the disfigurement of female breast with knife. The history of breast cancer is complex that includes the attempts to understand the nature of this disease to the hormone responsiveness, physical removal, chemotherapy to immunotherapeutic approaches. With scientific advancement we have evolved from surgery dominated treatment strategy to the targeted therapies with minimal damage. In this article we have explored the documented reports on breast cancer that helped us to evolve and develop novel intervention therapeutics. Further we have discussed the novel intervention strategies which will shape the future of breast cancer therapeutics.

Keywords: Breast cancer, targeted therapy, immunotherapy.

1. INTRODUCTION

Cancer is one of the leading causes of deaths of men and women in developed and developing countries and remained one of the challenges of modern society. Development of normal cell to cancer cell has multiple steps including altered signaling [1–6], oncogenic signaling [7,8], compromised apoptosis [9,10], therapy resistance [11,12] to DNA damage, targeted and non-targeted effects of radiation and chemotherapy [13–16] and compromised DNA repair [17,18]. Therapies strategies including chemotherapy [19,20], microRNA therapies [21,22], use of bacterial toxins for treatment [23–27], targeted and immunotherapies [28,29] are still trying to control the cancer-related deaths but struggling to reduce the poor prognosis of cancer. Further heterogeneity of cancer makes it more difficult to target, especially - breast cancer (BC) which has several subtypes [30,31]. The history of BC is as ancient as mummies and the understanding is developed from the theory of black fluid to cancer stem cell. We have better understanding about the BC now as ever before. The recombinant DNA technology helped a lot to decode the molecular signature of breast tumor cell that led to the differentiation of subtypes of BC. Moreover, we know the signaling cascade that regulates the cancer phenotypes [32,33]. But cancer cells are the smartest cell of body and they develop resistance to therapy with time. This gave a setback to the ongoing therapeutic programs as treatment resistant cancers are the major contributor in the clinical outcome. Triple negative breast cancer (TNBC), that is most aggressive form of BC adopted the strategy against
therapy by not expressing treatment responsive receptors. However, immunotherapy has provided scientific community a ray of hope to handle cancer in efficient and effective way. Harnessing host immune system is considered as one of the best strategy to counter BC. In this review article we have discussed the past and present of BC. Further, we discussed the present therapeutic interventions that are in clinics and novel intervention therapies which can shape the future of BC research.

2. History of breast cancer

From ancient times BC was known to mankind as it has been documented in almost every period of history. The earliest written records about BC came in existence after human started identifying organs of the body. Due to visible symptoms especially such as development of lumps with disease progression the BC have been recorded by physicians. As it was a matter of embarrassment and taboo the detection and diagnosis of BC was rare. Awareness and actively involvement of women brought this disease into the open in recent time. In the 1990’s the pink ribbon which is considered as the symbol of BC- brought a revolution against this disease. The Edwin Smith Papyrus an Egyptian around provides authentic accounts of BC around 3,000–2,500 B.C. The disease was believed to be incurable if it was “cool to touch, bulging and spread all over the breast” [34]. In 460 B.C., Hippocrates, known as the father of western medicine, defined BC as a humoral disease. He suggested that the human body consisted of four humors - phlegm, blood, yellow bile, and black bile. He advocated that the cancer was caused by the high amount of black bile. These were the early hypothesis developed in the area of cancer [35]. BC was believed to be hard tumor and if left untreated yield a black fluid. Later he named the cancer karkinos, a Greek word that means “crab,” as the tumors appeared to have tentacles similar to the legs of a crab. In A.D. 200, Galen also described the cancer that is caused by excessive black bile further he suggested that some cancer are more lethal than others [36]. Moreover, he advised several medications for BC such as licorice, opium, sulphur, castor oil, salves etc. In year 1680, a French physician Francois de la Boe Sylvius questioned the humoral theory of cancer. He suggested that cancer generates from a chemical process that transforms lymphatic fluids from acidic to acrid. Further in 1730s, Paris physician Claude-Deshais Gendron also questioned the systemic theory of Galen and suggested that cancer developed after nerve and glandular tissue mixed with lymph vessels. In 1757 a French physician, Henri Le Dran, advised that surgical removal of the tumor can help in the treatment of breast cancer, as long as the lymph nodes of armpits infected with tumor cells were removed. Further, Claude-Nicolas Le Cat suggested that surgical therapy was the only viable option to treat BC which led to the creation of the radical mastectomy or extensive removal of the breast.

3. Breast cancer sub-types

BC was considered to be a single disease, however growing body of evidence indicates that there are multiple subtypes of BC which are more or less aggressive and respond to different kinds of therapy. Further the risk factors can vary for each different subtype of BC. There are three basic groupings of BC on the basis of site of the tumor’s origin (ductal or lobular cancer); whether the tumor contained within the walls of the ducts or invasive and the reproductive status (pre-menopausal or post-menopausal) of the woman. Moreover, on the basis of biological markers, BC is classified into: basal, HER-2 over-expression, luminal A, luminal B, and unclassified [37,38]. Basal subtype of BC is also known as triple negative breast cancer (TNBC) as the tumor cell are negative for common three markers/receptors that is endrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2).

The percentage of TNBC is about 15% of BC diagnosis, however it has been known as most aggressive type of cancer with unresponsive to treatment that lead to poor prognosis [37]. Further, African American women are found to be more adversely affected by TNBC comparing to other races. HER-2 positive BC is suggested to have over expression of the HER-2 gene that promote the growth and aggressiveness of the disease. These kinds of tumors are responsive to targeted drug like Herceptin. The luminal A and B subtype’s tumors are positive to ER. The luminal A tumors grow slowly, however luminal B tumors have more rapid growth. Further luminal A tumors believed to have better prognosis than other subtypes. Advancement in the techniques of genomics and accumulating data also suggest that variations in gene (DNA) and their products might be associated with subtypes of BC [39]. A study that examined approximately 2,000 breast tumor samples based on clusters of genes either over or under-expressed in specific pattern suggested 10 separate subtypes of breast cancer [40]. Different subtypes of BC may have different risk factors. For instance, incidences of luminal B subtype...
of BC are high in women who gain substantial weight after the age of 18 [41]. Similarly, menopausal status of women can also influence the development of BC. For example, prolonged hormone replacement therapy (HRT) is believed to have connection with increased incidence of HER-2 overexpressing cancers in postmenopausal women. In addition, obesity and race have been associated with increased risk of aggressive TNBC [42].

4. Recent advancement and future directions

Deep understanding of signaling pathways and biology of BC have led to the development of novel innervation therapeutics to target the metastatic BC. In this section we highlighted some of the recent successes in BC drug which includes the strategies to overcome endocrine and human epidermal growth factor 2-neu (HER2) resistance and TNBC through novel therapies.

4.1. Targeting endocrine resistance

Several patients with BC develop early-stage ER-positive cancer and have risks of recurrence [43]. The available drugs have shown moderate effects and found to reduce the risk of recurrence marginally. The tumor of this nature goes in dormancy are show its symptoms when host compromise the immunity. Factors such as cancer stem cells, the tumor microenvironment, and immunity is believe to participate in this dormancy [44,45]. After recurrence the developed tumor cell show different genotype due to accumulated mutations compared to the tumor cells at the initial diagnosis [46]. Further the tumor did not respond to the standard endocrine therapies. Alteration in signaling such as phosphatidylinositol 3-kinase (PI3K)–Akt–mTOR(mammalian target of rapamycin) (mTOR) believed to contribute in resistance to endocrine therapy. The PI3K–Akt–mTOR signaling pathway are key intracellular signaling that promote cell growth and proliferation, and implicated in resistance to endocrine therapy [47]. Clinical trials of Oral Everolimus-2 (BOLERO-2) that inhibit mTOR found to improve the progression-free survival (PFS) in patients with ER-positive metastatic BC [48]. Further, the BOLERO-2 therapy is believed to be effective in patients whose cancer has progressed after treatment with a nonsteroidal therapies [49,50]. Several studies are also analyzing the effect of blockade of the PI3K–Akt–mTOR pathway in patients using PI3K inhibitors as well. Although the mutational status of PI3K was not found to be associated with progression free survival. Several other strategies explored to counter resistance to ER by targeting ER in novel ways such as use of fulvestrant that binds to the ER and promote its downregulation. Preclinical studies have indicated the antitumor effects of fulvestrant in BC [51]. Further, fulvestrant and Anastrozole Combination Therapy (FACT) have shown the beneficial effects against BC [52].

4.2. Anti-HER2 therapies

Since trastuzumab developed and approved the treatment of HER2-positive BC received extraordinary success [53]. In addition, several other drugs including lapatinib, pertuzumab, and trastuzumab emtansine (TDM-1), were approved to target HER2 positive BC [54,55]. However, BC evolved to counter the effects of these drugs and developed anti-HER2 therapy resistance. Several strategies have helped to understand the mechanisms that confer resistance, including the activation of HER2 mutations, loss of the epitope from the extracellular domain of HER2, reduced expression of HER2 expression, and activation of downstream signaling [56,57]. A study, analyzing the combination of everolimus to paclitaxel and trastuzumab in HER2-positive BC, who developed resistance to trastuzumab indicated 21.8% overall response rate (ORR), suggesting the biologic activity of the mTOR inhibitor [58]. Although, phase 3, BOLERO-1 trial, did not indicated an improved PFS in HER2-positive BC patients. In BOLERO-3 trial addition of everolimus to trastuzumab and vinorelbine were studied in metastatic HER2-positive BC, and found significant improvement in PFS [59]. The next-generation tyrosine kinase inhibitors (TKIs) of HER2 such as ONT-380 were developed and studied in combination with other anti-HER2 therapies. Application of afatinib, TKI of HER1 and HER2 demonstrated benefits in 46% of patients [60]. Further, anti-HER2 TKI neratinib, in both trastuzumab-naïve and trastuzumab-treated patients with metastatic HER2-positive BC with significant response rates [61].

4.3. Strategies against triple negative breast cancer

TNBC is one of the aggressive tumor phenotype have higher recurrence rates and lower prognosis [62]. Despite the therapeutic advancement there are no approved therapies for this subtype of BC. Though, there are several novel strategies that are still in development phase. The application of platinum agents in TNBC have been explored and
found to be attractive considering the metastatic nature of this cancer [63]. Further platinum-based chemotherapy is shown to improve the survival of patients with metastatic TNBC [64]. The TNBC Trial (TNT), conducted in patients with metastatic TNBC to carboplatin vs docetaxel had no statistically significant PFS. Though, the patients with breast cancer susceptibility gene (BRCA) germline mutations, the carboplatin therapy improved the ORR than double that of the docetaxel arm (ORR, 68.0 vs 33.3%; P = .03). Further, understanding of the patients that are most likely to be benefited from platinum-based therapy can improve the efficacy of treatment. Application of poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors has also been suggested to have potential to target TNBC, in women with BRCA germline mutations. Iniparib, known as PARP inhibitor, showed improved PFS (3.6-5.9 months) and OS (7.7-12.3 months) in metastatic TNBC [65,66] However, it has been demonstrated that iniparib has weak, if any PARP, inhibitory effects [67]. This study put a question mark on the development in PARP inhibitors for BC. Few agents including olaparib and veliparib are generated interest in research community with their therapeutic efficacy [68]. Moreover, for ovarian cancer patients with BRCA germline mutation PARP inhibitor, olaparib, has generated enough buzz and is in phase 2 study [69]. Another lucrative strategy for targeting TNBC is through the glycoprotein NMB (gpNMB) that expressed in nearly 40-60% of BC. A phase 1/2 study is still ongoing and investigating the therapeutic efficacy of anti-gpNMB monoclonal antibody conjugated to monomethyl auristatin in patients with metastatic BC [70].

4.4. Immunotherapies

Immune system of the host has the capacity to identify cancer antigens and destroy it. However, tumor cancer-induced immunosuppression keeps the immune system in check and allows rampant cancer growth [71]. Thought, in recent years the success of immune checkpoint blockade has restored the hope that that immune therapy is a viable strategy against cancer. Cytotoxic T-lymphocyte antigen (CTLA) inhibitors have shown their antitumor activity in melanoma [72]. Further, blockade of the programmed cell death 1 (PD-1) and its ligand PD-L1 has also been demonstrated to confer antitumor activity in several cancers [73]. Interestingly, the efficacy of single checkpoint blockade have shown moderate activity in some patients, however, combination checkpoint blockade with CTLA and PD-1 inhibitors shown synergistic effects with an ORR of 40%.

Moreover, in 31% of patients significant reduction in their tumors was observed by 12 weeks, suggesting the combination therapy improve antitumor responses [74]. As for as TNBC is concerned nearly 20% of patients express PD-L1, which is linked with poor prognosis. Understanding the role of PD-L1 can be an attractive strategy [75]. Interestingly, anti-PD-L1 monoclonal antibody, pembrolizumab, demonstrated clinical activity in women with TNBC.

5. CONCLUSION

Developing targeted therapies against different subtype of breast cancer is the utmost priority for researchers. Since ancient time, breast cancer fascinated mankind due to its complicity and lethal effects. Although, it took a lot of time to understand the biology of breast cancer but we made decent progress in current time. Although, many times treatment was seemed very near but due to the existence of different subtypes and heterogeneity in breast cancer, we struggled to achieve the expected success. One of the problem with breast cancer is the presence of different subtypes that need separate attention and treatment strategies. In such situation finding one solution for all subtype is tough. However, the exploitation of host immune system against cancer can be the better strategy as the immune system has immense potential to destroy the tumor cell. The immunotherapeutic strategies such as activation of immune system by blocking checkpoint inhibitor have shown its potential in cancer treatment. Hopefully, in near future we will witness the novel targeted and immunotherapeutic approaches that may reduce the overall outcome of death caused by breast cancer.

Conflicts of Interest

There are no conflicts of interest.

References


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